CC/MIN/2019/03

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Minutes of the meeting held at 10.30am on Thursday 7th November 2019 at Public Health England, Centre for Radiation, Chemical and Environmental Hazards, Harwell Campus, Didcot, Oxon, OX11 0RQ.

Present

Chair:	Professor D Harrison	
Members:	Mr D Bodey	
	Dr G Clare	
	Dr J Doe	
	Dr R Haworth	
	Dr R Kemp	
	Dr D Lovell	
	Dr L Rushton	
	Dr R Waring	
	Professor H Wallace	
Secretariat:	Miss B Gadeberg	PHE Scientific Secretary
	Ms C Mulholland	FSA
Assessors:	Dr G McEneff	BEIS-OPSS by Skype
	Dr H McGarry	HSE by teleconference
	Mr N O'Brien	VMD
	Dr O Sepai	PHE
Officials:	Dr M Jacobs	PHE (Item 4)
	Mr L Johnstone	BEIS-OPSS by Skype
	Dr T Marczylo	PHE (Item 9)
	Mr S Robjohns	PHE
Invited Experts and Contractors:	Dr R Bevan	IEH Consulting
	Dr S Bull	WRC Ltd
	Dr G Hendriks	Toxys
	Dr P Rumsby	IEH Consulting
	Dr K Vassaux	for WRC Ltd by Skype (Item 9)
	Ms P van Rossum	Toxys
Observers:	Professor L Levy	IEH Consulting
	Ms A van der Zalm	PETA International Science Consortium Ltd

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ITEM 1: Announcements and apologies for absence

1. The Chair welcomed Members, and other attendees to the meeting. Apologies were received from Professor N Pearce, and Dr D Gott (FSA Secretariat) who was represented by Ms C Mulholland. Assessors Dr W Munro (FSS), Dr H Stemplewski (MHRA), and Dr L Lawton (Defra) also sent apologies.

2. The four vacancies on the Committee were advertised over the late summer months. Interviews would be held in due course and the Committee would be kept informed when new Members were appointed.

3. The Department of Business, Energy and Industrial Strategy, Office for Product Safety and Standards (BEIS-OPSS) officials joined the meeting for the first time and explained its remit. Aspects of relevance to the Committee including the assessment of chemicals in consumer products, especially cosmetics and toys, assessment of nanomaterials and other ingredients in cosmetics, and recycled materials in consumer products and exposure to unknown chemicals.

4. Members were reminded to declare any interests they may have in an item before its discussion.

ITEM 2: Minutes of meeting held on 16th July 2019 (CC/MIN/2019/02)

5. No amendments were required to the presented minutes. The minutes for Item 4 would be agreed by correspondence after the meeting.

ITEM 3: Matters arising

Item 6 – Scoping paper on the synthesis and integration of epidemiological and toxicological evidence in risk assessments

6. COC Members had been invited to participate in a working group on this topic by correspondence after the July COC meeting. Members joining the group had been invited to join an initial teleconference, which would take place on 19th November 2019.

Item 7 – Development of a framework for consideration of risk due to less than lifetime exposure

7. Members had commented on a draft paragraph by correspondence after the July meeting, and the statement was being finalised for Chairs approval.

ITEM 4: Update on the validation of the ToxTracker Assay – presentation by Dr Giel Hendriks (Toxys)

8. The ToxTracker assay is a stem cell-based screening platform which utilises six unique reporter cell lines to detect carcinogenicity and provide information relating to the mode of genotoxic action. The COC last evaluated the technology in 2017 and since that time ToxTracker has undergone further development. Dr Giel Hendriks, Toxys, who has developed the assay presented an update with a specific focus on non-genotoxic modes of action.

9. The reporter cell lines detect changes that may indicate carcinogenicity, including, two types of DNA damage, activation of p53, oxidative stress and/or ROS production, and protein damage. ToxTrackerACE (Aneugen and Clastogen Evaluation) also allows the detection of aneugenicity leading to cell cycle block and polyploidy. Biomarkers specific for non-genotoxic carcinogens have been investigated, and PCA analysis of differentially expressed gene data showed that non-genotoxic carcinogens and non-genotoxic non-carcinogens grouped together, meaning that no specific marker for non-genotoxic carcinogens is apparent.

10. To date, a large number (>1000) and range of substances have been tested using ToxTracker including single molecules, polymers, complex mixtures, nanomaterials, and intermediates. As such, there is a growing trend to include the assay for early screening and hazard identification purposes, in addition to its use in follow up testing, identifying mode of action, for quantitative dose response modelling, TTC and for WoE considerations. Technical in-house validation of ToxTracker indicated sensitivity and specificity to be around 90% and this was supported by the findings of a small inter-laboratory validation exercise (2 laboratories). A much larger inter-laboratory validation exercise (8 independent laboratories in the US, EU and Japan) was in progress, with the aim of assessing adoption of the assay by ECVAM and OECD, with findings expected to be reported in early 2020.

11. Following the presentation, clarification was sought as to the reasoning for use of mouse rather than human stem cells, as the basis of the ToxTracker assay. It was confirmed that the stem cells were included as they were considered of greatest relevance to cancer; but targeted assessment had found that assays carried out using human stem cells provided the same findings as mouse stem cells. It was also noted that both mouse and human stem cells did not have metabolic capacity, which was potentially were differences between species could arise.

12. The future regulatory use of ToxTracker was also considered. At the present stage of development and validation there is no intention to replace standard assays, though ToxTracker is finding use as a follow up to explain equivocal findings. The assay cannot replace mutation assays, however there may be scope for it to replace the *in vitro* micronucleus assay, especially as it also shows good correlation with the *in vivo* micronucleus assay. Once the validation exercise was complete, discussions would be held with OECD around regulatory acceptance and where to position its use. A potential wider use of the ToxTracker assay as an initial screening tool for characterisation of AOPs to detect general toxicity and not just carcinogenicity was also considered by the COC.

13. In conclusion, it was agreed that the COC would keep a watching brief on developments with the ToxTracker platform, particularly with regards to regulatory acceptance. Further exploration of its use as an initial screen for general toxicity and characterisation of AOPs was also considered to be of particular value.

ITEM 5: Horizon scanning 2019 (CC/2019/13)

14. No interests were declared for this item.

15. This paper presented the formal annual horizon scan, with the list of topics from the 2018 list, an update on the work of IARC and the EU Scientific Committees, and an overview on the balance of expertise of the Committee.

16. A short update was given on recent IARC conclusions, which could be relevant to bear in mind during chemical risk assessment, this included a statement regarding the role of being overweight and/or obese in cancer development, published in August 2016, and a short paper on the carcinogenicity of shift work, published in July 2019 in Lancet Oncology, for which a monograph would be published in mid-2020. The mechanism behind the epidemiological findings for shift workers (e.g. airline pilots and air crew) is currently undefined, and it was suggested that COC could as necessary play a role in interpreting this.

17. The advantages and disadvantages of epidemiology studies in general were discussed and it was agreed that the importance of epidemiology as part of the risk assessment process was being increasingly recognised in the wider community. Epidemiology is currently the only tool that takes all exposure routes into consideration and additionally, there is no requirement to extrapolate findings from one species to another.

18. One Member was part of the Industrial Injuries Advisory Council and noted there were a number of topics likely to be on which the COC might be able to provide specialist input on any potential role of chemicals in carcinogenicity.

19. It was agreed that the ToxTracker assay should also be kept under review as it progressed through the OECD process. With respect to animal and in vitro data, big data and artificial intelligence, it was agreed that the Committee should take a more holistic view to recognise that the Committee's focus was more on evaluating any evidence available for a chemical to assess its potential for carcinogenicity. An area of particular interest would be investigating the modes of action of chemicals to assess how they might interact either with other substances or with the carcinogenic process.

20. A short overview of the immunological and stromal cell modulations relevant to cancer risk was presented by the Chair. The importance of considering the influence of the immune system and pre-tumour cell microenvironment on the development of cancer was emphasised. For such systems to be addressed however, current testing strategies and approaches to risk assessment may need to be reconsidered. The dynamic nature of cells within the tumour cell microenvironment and its impact on the repair of damaged cells was also highlighted as having a key role in tumour cell development. Lastly, it had been known for some time that antibiotics could change the impact of certain cancer drugs which is thought to be due to alterations in the microbiome; thus consideration of the impact of the microbiome on cancer cell development was also important.

21. There was agreement for COC to acknowledge the importance of the tumour microenvironment in its future strategic planning. A position paper to explore available information to address these issues and where COC influence can best be targeted, was agreed as an initial way forward. In the longer term, effects of infections could also be captured.

22. Following the discussion, it was agreed that the topics of priority for the coming year would be:

- IARC assessment of shift work and how that might affect assessment of chemicals and carcinogenicity
- View on the future of assessment of carcinogenicity including use of animal models, in vitro and in silico data as well as new approaches encompassing artificial intelligence and analysis of big data.
- The cellular microenvironment and role in carcinogenicity

23. The potential for an increase or change in work of the Committees following EU Exit was discussed.

ITEM 6: Guidance Statement G05: Points of departure and potency estimates – first draft revision (CC/2019/14)

24. No interests were declared for this item.

25. G05 “Defining a Point of Departure and Potency Estimates in Carcinogenic Dose Response” forms one of a series of Guidance Statements from COC that outlines its strategy for carrying out risk assessments of chemical carcinogens. An updated version of G05 was agreed by the COC in September 2018, awaiting a full review to be undertaken when EFSA published further guidance on the TTC approach. This guidance was published by EFSA in April 2019, and the paper presented was a first draft revised guidance statement with all sections having been reviewed and updated as needed.

26. There was agreement from the COC that the document should be further modified, in particular, to remove historical data and references and to rationalise section lengths. It was also considered that an introductory section be added to place the content in context of the risk assessment process as a whole. This should also convey that the tools outlined in G05 are those available for use should the risk assessor consider them appropriate. This would produce a stand-alone document which could be read in isolation, but which also provided links to other COC Guidance Statements for the remaining aspects of the risk assessment process.

27. Following amendment, it was agreed that a second draft of the revised guidance statement would be presented to the Committee at the next meeting in March 2020.

ITEM 7: Guidance Statement G01: A strategy for risk assessment of carcinogenicity – second draft revision (CC/2019/15)

28. No interests were declared for this item.

29. Draft updated versions of G01, which provides overarching guidance of COC’s strategy for assessment of carcinogenicity, were presented to COC in March and July 2019. This paper contained the revisions made to the draft document in addressing comments from the July 2019 meeting. This included an extended

discussion of the current and evolving thinking about carcinogenicity ('Evolving Approaches') as well as providing a description of the testing strategies presently used.

30. The amended "Evolving Approaches" section was considered to be appropriate and to reflect the current philosophy of the Committee. As this section was likely to be read by non-experts, the lay members of the Committee were asked to provide feedback on its 'understandability' in that context. Some further minor amendments to the second draft revision were also discussed.

31. Following amendment is was agreed that the third revised draft would be circulated to members for comment by correspondence and then signed off by the Chair.

ITEM 8: Guidance Statement G08: Risk assessment of the effects of combined exposure to multiple chemicals on carcinogenicity – first draft revision (CC/2019/16)

32. No interests were declared for this item.

33. A review outlining developments in the risk assessment of combined exposure to multiple chemicals was considered by the Committee in November 2018. It was agreed that these developments, together with an increasing knowledge of cancer aetiology, could provide a cancer endpoint-specific approach for the risk assessment of the combined exposure to chemicals on carcinogenicity. In March 2019, a revised document was considered by the Committee, and it was agreed that a revised Guidance Statement (G08) should be produced that considered the potential for a novel carcinogen-specific risk assessment paradigm for combined exposures to multiple chemicals, including carcinogens.

34. The paper presented the first draft revision of G08. The general structure and text were considered appropriate and members made several specific suggestions to aid clarity. Some additional references were also discussed for potential inclusion.

35. Following amendment of G08, it was agreed that the second revised draft would be circulated to members for comment and then signed off by the Chair.

ITEM 9: Potential toxicological risks from electronic nicotine and non-nicotine delivery systems (E(N)NDS – e-cigarettes) – update of available data on carcinogenicity (CC/2019/17)

36. No interests were declared for this item.

37. The COT is currently considering the potential toxicological risks of electronic nicotine (or non-nicotine) delivery systems (E(N)NDS). A number of papers relating to the carcinogenicity of E(N)NDS were presented and discussed by the COC in July 2018. This paper presented two studies identified from an updated literature search for the COC to consider whether any new information on potential carcinogenicity of E(N)NDS should be highlighted to the COT.

38. The two studies were discussed; one was a study in mice and the other an *in vitro* study. It was considered that there were a number of substantial confounding

issues, including methodological ones, that prevented any robust conclusions being drawn specifically from these two papers. Overall, COC agreed that the papers did not alter their previous conclusions on the potential carcinogenicity of E(N)NDS. This conclusion would be fed back to the COT.

ITEM 10: Any other business

COC meeting dates for 2020

39. Dates for COC meetings in 2020 had been circulated. There was some discussion over availability of Members for the July and November dates. This would be clarified by correspondence after the meeting and dates confirmed.

Horizon scanning for COT and COM

40. It was suggested that as COT and COM also conduct horizon scanning exercises, it would be helpful if these could be shared across the Committees so there could be mutual awareness of priorities across the three Committees.

ITEM 11: Date of next meeting

41. The next meeting would be held on 12th March 2020, at PHE Chilton.